Statistical Analysis Plan

Protocol Title:	A 40 to 52-Week Open-Label Extension Study to Evaluate TNX-102 SL Taken Daily at Bedtime in Patients with PTSD
Protocol Number:	Protocol No. TNX-CY-P306 (05JUN2019); Amendment 4, Dated 05JUN2019
Investigational Product:	Tonmya®/TNX-102 SL (cyclobenzaprine HCl sublingual tablets), 2.8 mg
Dose	5.6 mg taken daily at bedtime as two 2.8 mg sublingual tablets
Phase:	3
Sponsor:	Tonix Pharmaceuticals, Inc. [redacted]
SAP Author:	[redacted]
SAP Version:	Final v1.0
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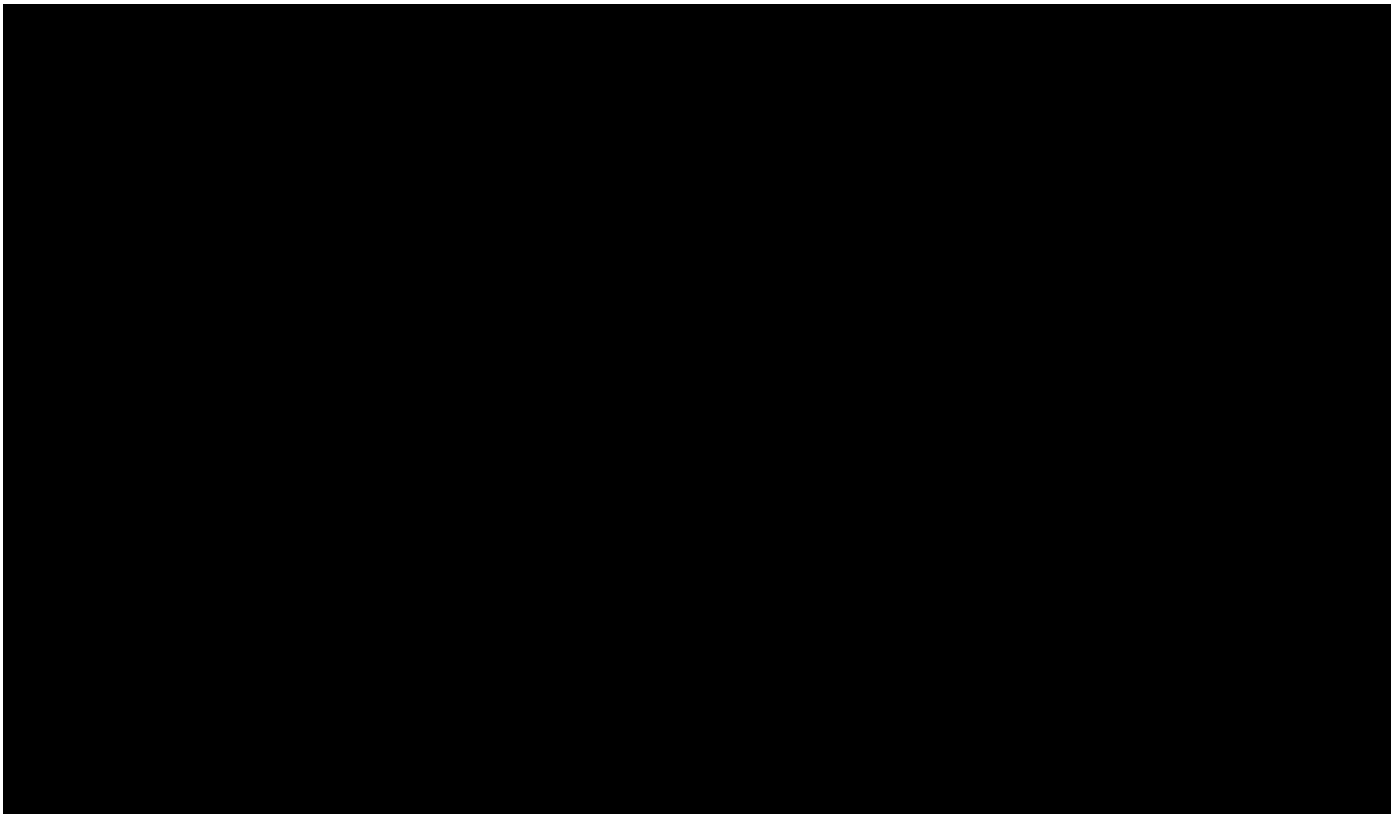

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ABBREVIATIONS

ABBREVIATION	DEFINITION OR DESCRIPTION
AE	Adverse Event
ADaM	Analysis Data Model
BDI-II	Beck Depression Inventory–II
BMI	Body Mass Index
CA-AF	Criterion A – Assessment Form
CAPS-5	Clinician Administered PTSD Scale (for DSM-5)
CGI-I	Clinical Global Impression- Improvement from Initiation of Treatment
CI	Confidence Interval
CMH	Cochran Mantel Haenszel
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (Version 4)
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (Version 5)
ECG	Electrocardiogram
EDC	Electronic Data Capture
e.g.	*Exempli gratia* (for example)
EMA	European Medicines Agency
ET	Early Termination
FDA	Food and Drug Administration
HCl	Hydrochloride
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
i.e.	*id est* (that is)
IWRS	Interactive Web Response System
LS	Least Squares
MAR	Missing at Random
MDE	Major Depressive Episode
MedDRA	Medical Dictionary for Regulatory Activities
Military-Related	Related to service in any branch of the armed services (active or veteran), or as a military contractor
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed Model Repeated Measures
N, n	Number (of participants)
NEAE	Newly-Emergent Adverse Event
NIH	National Institutes of Health
PGIC	Patient Global Impression of Change Scale
PROMIS	Patient-Reported Outcome Measurement Information System
PTSD	Posttraumatic Stress Disorder
REML	Restricted Maximum Likelihood
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SD	Standard deviation
SDS	Sheehan Disability Scale
SDTM	Study Data Tabulation Model
SE	Standard Error
SL	Sublingual
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TNX-102 SL	Cyclobenzaprine HCl sublingual tablets
WHO-DD	World Health Organization Drug Dictionary

1. OVERVIEW

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for protocol TNX-CY-P306: A 40 to 52-Week Open-Label Extension Study to Evaluate TNX-102 SL Taken Daily at Bedtime in Patients with PTSD; Amendment 4, Dated 05JUN2019.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by FDA, European Medicines Agency (EMA), and International Council for Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association and the Royal Statistical Society, for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc, or unplanned exploratory analysis performed will be clearly identified as such in the final CSR.

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The reader of this SAP is encouraged to also read the clinical protocol, and other identified documents, for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

For purposes of clarity, all analyses in this SAP refer to data collected in study TNX-CY-P306, except to the extent that some baseline measures may have been collected in a prior study (Section 7.1) and except for the analyses set forth in Section 12.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of the study is to evaluate the long-term safety of TNX-102 SL taken daily at bedtime over an additional 40 to 52 weeks in patients with PTSD who have participated in a double-blind lead-in HONOR study (TNX-CY-P301) and possibly a 12-week open-label extension study TNX-CY-P303.

2.1.2 Secondary Objectives

The secondary objective of the study is to evaluate the long-term effect of TNX-102 SL taken daily at bedtime over an additional 40 to 52 weeks in patients with PTSD who have participated in a double-blind lead-in HONOR study (TNX-CY-P301) and possibly a 12-week open-label extension study TNX-CY-P303.

2.2 Study Endpoints

2.2.1 Efficacy Endpoints

Comparisons will be made at each study week of data collection to the baseline of this study.

Efficacy endpoints include:

- Average CGI-I score (scored 1-7)
- Proportion of patients with a CGI-I score of "very much improved" or "much improved"
- Change from baseline in the SDS total score
- Change from baseline in the individual items assessed using the SDS
- Change from baseline in patients' quality of sleep using the PROMIS Sleep Disturbance scale
- Change from baseline in BDI-II score
- Change from week 28 to week 40 in PCL-S
- Change from week 28 to week 52 in PCL-S (Track B subjects only)
- Change from week 40 to week 52 in PCL-S (Track B subjects only)

2.2.2 Safety Endpoints

Safety will be assessed by:

- Adverse events (AE) and serious AEs (SAEs) throughout the entire duration of the study, including detailed assessment of AEs involving the oral cavity.
- Changes from baseline in clinical laboratory test results.
- Changes from baseline in vital signs and weight.
- Change from baseline in BDI-II.
- Suicidal ideation or behavior as reported on the Columbia-Suicide Severity Rating Scale (C-SSRS).

3. OVERALL STUDY DESIGN AND PLAN

This is a 40 to 52-week, multicenter, open-label extension study designed to establish long-term safety exposure and to examine the long-term effect with daily bedtime dosing of TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) in patients with PTSD. This study will be conducted at approximately 35 sites in the United States (US).

Patients who have either: (a) completed the double-blind lead-in study (P301/HONOR study), and completed or are active (at the time of study discontinuation) in the 12-week open-label extension study, P303; or (b) are enrolled in the double-blind lead-in study (P301/HONOR study) that has been discontinued due to results of an interim analysis, will be eligible. For Track A patients, this extension study consists of 5 in-clinic visits, including the Screening/Baseline visit and visits after 7, 16, 28, and 40 weeks of treatment (Visits 3-6). There will also be a telephone visit after 2 weeks of treatment (Visit 2) for patients enrolling from the double-blind lead-in study, P301/HONOR. The total treatment duration of this study will be 40 weeks for patients enrolled under Track A criteria, and 52 weeks for patients enrolled under Track B criteria. Therefore, the maximum total duration of continuous treatment with TNX-102 SL could be approximately 64 weeks for those patients assigned to TNX-102 SL in the lead-in HONOR study who then also completed the 12-week open-label extension study P303. For patients enrolling from the open-label extension study, P303 (Track A), there is no need to repeat assessments at Visit 1 for this study, if the patient enrolls and initiates study treatment within fourteen days of completing the 12-week open-label extension study P303. For patients who are active in the double-blind lead-in study, P301/HONOR (Track B), all Baseline procedures and assessments will be completed at Visit 1.

After the patient has participated in the lead-in HONOR study or the open-label extension study, P303, and has consented to participate in this open-label extension study, patients will be dispensed a 7-week supply of open-label TNX-102 SL tablets (3 bottles) and will be instructed to take 2 tablets of study drug sublingually daily at bedtime, starting on the evening of Visit 1. A phone visit will be completed after 2 weeks of treatment for patients enrolling from the double blind lead-in study, P301/HONOR. All patients will return to the study center for safety and efficacy assessments at Weeks 7, 16, 28, and 40 (or early termination). Patients enrolled under Track B criteria will continue to dose for an additional 12 weeks and have the last study visit at Week 52. Patients will return their TNX-102 SL medication (including empty bottles) at these visits. Patients will also receive a 9-week supply of TNX-102 SL (4 bottles) at the Week 7 visit, and a 12-week supply (5 bottles) at the Week 16, 28 and 40 (Week 40 for Track B patients only) visits. Patients will be allowed to take other medications deemed appropriate by their health care providers to manage their PTSD and other conditions, including currently approved PTSD therapies.

3.1 Selection of Study Population

For a complete list of inclusion and exclusion criteria please refer to the protocol.

3.2 Method of Treatment Assignment and Randomization

All patients will be assigned to TNX-102 SL, 5.6 mg regardless of which treatment arm they were randomized to in the lead-in study. No patients or site personnel will know what the prior treatment was in the double-blind lead-in study.

Throughout this document, when describing analyses performed by treatment group, this will refer to the treatment that the subject was randomized to in the double-blind lead-in study.

4. ANALYSIS AND REPORTING

4.1 Final Analysis

All final, planned analyses will be performed after the last participant has completed all study assessments, all relevant study data have been processed and integrated into the analysis database, and the database has been locked.

5. SAMPLE SIZE DETERMINATION

No sample size calculations were made for this study as it is a follow-on, open-label study. The sample size for this study will depend upon the number of patients who complete the lead-in study, remain eligible for entry, and indicate willingness to participate in this extension study.

6. ANALYSIS POPULATIONS

The following analysis populations are planned for this study:

- **Safety Population (SAFETY):** All participants who receive at least 1 dose of study drug in Study TNX-CY-P306. Participants who are issued study drug, but return 100% of it (i.e., none consumed) will be excluded from the Safety Population; likewise, participants that have no follow up following receipt of study drug to indicate they took drug are excluded. All analyses will be performed using this population, unless otherwise specified in this SAP.

7. GENERAL ISSUES FOR STATISTICAL ANALYSIS

7.1 General Statistical Methodology

Descriptive summaries will be provided where appropriate for each of the primary and secondary variables. In general, tables will summarize data by treatment group as defined in Section 3.2 and visit.

All tables will be completed for the Safety Population unless otherwise specified.

Continuous, quantitative, variable summaries will include the number of participants (N) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum.

Categorical, qualitative, variable summaries will include the frequency and percentage of participants who are in the particular category. In general, the denominator for the percentage calculation will be based upon the total number of participants in the study population for the treatment group unless otherwise specified.

Unless otherwise noted, baseline values are defined as the last non-missing measurement prior to the first dose of open-label study drug in Study TNX-CY-P306. Change from baseline will be defined as the post-baseline visit value minus the baseline value.

ET participants will only be followed if required to monitor an on-going adverse event or other condition.

Participants are not supposed to change study sites; however, should this be necessary to allow a participant to continue in the study, participants will be analyzed under the site where they were initially enrolled.

Study day after first dose is defined as assessment date – first dose date +1. Dates prior to first dose are defined as assessment date – first dose date. Note that the protocol refers to "Day 0"; for the purposes of the datasets and analyses, this would appear as day 1.

All analyses will be performed using Statistical Analysis System (SAS®) Software version 9.4 or later.

Unless otherwise noted, 95% confidence intervals will be presented for statistical tests.

7.1.1 Adjustments for Multiplicity and Other Alpha Control

7.1.1.1 Multiplicity

No adjustments will be made from multiplicity and all p-values will be nominal.

7.1.2 Data Handling for Participants Who Discontinue Study Drug or Withdraw from the Study

Participants who withdraw/drop out from the study will have their ET visit data collected and included in the analysis based on the closest visit window (Week 7, 16, 28, 40, or 52). Visit windows will be assigned by splitting the periods between visits at the midpoint between the visits. If more than one record falls within the window, the one closest to the target date will be used in the analysis, with preference given to the scheduled visits in the case of equidistant visits.

7.2 Efficacy Assessments

There is no formal testing order to the efficacy assessments in this protocol; however, they are described below in approximate order of importance.

7.2.1 Clinician Global Impression of Improvement (CGI-I)

The CGI-I will be completed by an Investigator to evaluate the participant's status since the start of the current study (P306). The CGI-I will be completed at each in-clinic visit after baseline. It will be the responsibility of the Principal Investigator or his qualified designee to assess change in the subject's overall status and answer the following question:

Since the initiation of treatment in P306, the participant is:

1 = Very much improved
2 = Much improved
3 = Minimally improved
4 = No change
5 = Minimally worse
6 = Much worse
7 = Very much worse

The primary analysis of CGI will treat it as a continuous variable (scored 1-7 as above). There will be an additional outcome presented where a responder on the CGI-I is defined a participant who is scored as 'Very much improved' or 'Much improved' and compared between the study arms.

7.2.2 Sheehan Disability Scale (SDS)

The SDS scale is a self-report questionnaire that was designed to assess the participant's view of the degree to which symptoms have disrupted work/school, social life/leisure activities, and family life/home responsibilities during the previous 2 weeks (Sheehan & Sheehan, 2008). In addition, the SDS asks the participant to provide the number of days of work/school lost as well as unproductive days in the past two weeks. The SDS scale will be completed by the participant at Baseline and after 7, 16, 27, and 40 weeks, plus 52 weeks for Track B participants. A total score will be calculated summing the three individual 11-point (0-10) scales. For participants that do not respond to the work/school disruption because the participant checked the box indicating he/she has not worked or attended school for reasons unrelated to the disorder (PTSD), the total score will sum the other 2 domain questions and multiply by 1.5 (rounding up to the nearest whole number) to maintain the scale of 0-30 for the total score. Participants with missing values on the other items will be missing for the total.

7.2.3 Other Efficacy Outcomes

7.2.3.1 PROMIS Sleep Disturbance Instrument

PROMIS refers to the Patient-Reported Outcome Measurement Information System (www.nihpromis.org), a National Institutes of Health (NIH)-funded initiative to develop instruments to be used across chronic conditions.

The PROMIS sleep disturbance scale (short form 8a) will be assessed at Baseline and after 7, 16, 27, and 40 weeks, plus 52 weeks for Track B participants.

The sleep disturbance scale will be calculated summing the individual item scores of the 8 items. These summed scores will be transformed to T-scores using the published conversions (see Section 15.2).

7.2.3.2 BDI-II

The Beck Depression Inventory (BDI-II) is a 21-item measure of the severity of current depressive symptoms, extensively validated for use in both medical and mental health populations. While this instrument does not provide a psychiatric diagnosis of depression and has considerable overlap with PTSD associated symptoms, it does provide a continuous scale for measuring changes in the severity of symptomatology. The BDI-II will be completed by the participant at all in-clinic visits.

7.3 Safety Assessments

Safety will be assessed by:

- AE and SAEs throughout the entire duration of the study, including detailed assessment of AEs involving the oral cavity.
- Changes from baseline in clinical laboratory test results.
- Changes from baseline in vital signs and weight.
- Change from baseline in BDI-II (see Section 7.2.3).
- Suicidal ideation or behavior as assessed by the C-SSRS.

7.3.1 Adverse Event and Prior/Concomitant Medication handling conventions

To handle missing or partial prior/concomitant medication dates, the following rules will be applied.

For partial start dates:

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then:
    a. If the year matches the year of the first dose date, then impute the month and day of the first dose date.
    b. Otherwise, assign “January.”
3. If the day is unknown, then:
    a. If the month and year match the month and year of the first dose date, then impute the day of the first dose date.
    b. Otherwise, assign “01.”

For partial end dates:

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then assign "December."
3. If the day is unknown, then assign the last day of the month.

After implementing the rules above, to determine whether medications with missing start or stop dates are prior or concomitant medications, the following strategy will be used:

1. If the start date and stop date are both missing, then the most conservative approach is taken and the medication is considered to be a concomitant medication.
2. If the start date is missing but the stop date is not missing and is after the day of first study dose administration, then the most conservative approach is taken and the medication is considered to be concomitant.
3. If the start date is missing but the stop date is not missing and is on or before the day of first study dose and after the date of signed informed consent, then the medication is considered to be a prior medication.
4. If the start date is not missing but the stop date is missing, then the most conservative approach is taken and medication is considered to be concomitant.

The missing severity of an AE will be imputed to "severe"; the missing relationship to study drug of an AE will be imputed to "possibly related".

8. STUDY PARTICIPANTS AND DEMOGRAPHICS

8.1 Disposition of Participants and Withdrawals

The numbers and percentage of participants entering, completing the study, and withdrawing from the study, along with reasons for withdrawal, will be tabulated overall and by treatment group. This summary will be based on all participants who have data entered into the database.

8.2 Protocol Deviations

Protocol deviations will be checked on complete data for all participants, determined during a data review meeting before database lock and the final analysis.

Protocol deviations will be summarized by type and by treatment group for the Safety population. Protocol "violations" are not differentiated from deviations; instead, each deviation is identified either as "major" or "minor" depending upon its potential impact upon the integrity of the study data or the participant's well-being.

Individual participants with protocol deviations will be listed.

8.3 Demographics and Other Baseline Characteristics

Descriptive summaries of the demographic and other baseline characteristics will be completed for all participants in the safety population by treatment groups, unless otherwise specified.

Descriptive summaries of demographic and other baseline conditions will include:

- Demographics (age, gender, race/ethnicity, height, weight, body mass index (BMI), family status, education, presence of current MDE, current nicotine, alcohol and THC usage, and employment status).
- CAPS-5 Assessment (Diagnostic version)

Other assessment's baseline values will be reported with their respective follow-up measures.

Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 and summarized by System Organ Class (SOC) and Preferred Term using frequency counts by treatment group. Note that the medical history, demographics, and baseline characteristic data are collected in the lead-in study; this analysis displays that information for the population of subjects that entered this study.

9. EFFICACY ANALYSES

9.1 Continuous Outcomes

The mean change from baseline in the continuous outcome of interest will be analyzed using a restricted maximum likelihood (REML) based repeated measures approach, without imputation. The model will include all participants in the safety population. The dependent variable will be the observed change from baseline with respect to each outcome at each post-randomization visit.

9.1.1 Efficacy Analysis Model

A Mixed Model Repeated Measures (MMRM) analysis will be performed for the change from baseline in separate, independent models for each endpoint. The model will include all participants in the safety population, and the dependent variable will be the observed change from baseline the outcome of interest at each post-randomization visit. Covariates in the model will include the fixed categorical effects of treatment group exposure, site, sex, visit and treatment group by visit interaction, as well as the continuous fixed covariates of baseline score and baseline score by visit interaction. An unstructured covariance matrix will be used to model the within-subject variance-covariance errors. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Should the unstructured model fail to converge, an autoregressive AR(1) covariance structure will be attempted, then finally compound symmetric should AR(1) not converge.

The least squares means and 95% confidence intervals (CIs) will be calculated for the treatment difference between the subjects that received TNX-102 SL in a prior study and those that did not.

These endpoints to be analyzed with this model will include:

- CGI-I score.
- Change from baseline in SDS total.
- Change from baseline in participants' quality of sleep using the PROMIS Sleep Disturbance scale.
- Change from baseline in the disruption of work/school activities assessed using the SDS.
- Change from baseline in disruption of social life/ leisure activities assessed using the SDS.
- Change from baseline in the disruption of family life/home responsibilities assessed using the SDS.
- Change from baseline in BDI-II score.

The model will be changed to include the corresponding baseline value of each the endpoints. To estimate the difference between the treatment arms in CGI-I score (which does not have baseline assessments), the same method will be used, however, with the observed baseline response and associated interactions removed from the list of covariates. All visits will be included in the analysis. P-values from these comparisons will be considered nominal.

For each outcome, descriptive statistics (mean, SD, median, minimum and maximum) will be reported as well as LS means, standard error (SE) and p-values comparing the arms at each visit. In addition, for the SDS, the frequency of participants not working or attending school due to reasons unrelated to PTSD will be reported overall and within each visit.

9.1.2 Categorical outcomes

The proportion of responders (participants with a CGI-I score of "much improved" or "very much improved") over time will be reported with the number and percentage of participants in each group (participants that received TNX-102 SL in a prior study and those that did not). Participants with missing data will be analyzed as though they are non-responders. A difference in proportions Z-test and the corresponding two-sided 95% CIs will also be reported. Two-sided p-values for the test of no difference between the groups will be provided.

10. SAFETY AND TOLERABILITY ANALYSIS

The safety analysis will be run on the Safety Population. The analysis of safety assessments in this study will include summaries of the following safety and tolerability data collected for each participant:

- Adverse Events
- Clinical Laboratory Investigations
- C-SSRS
- Vital Signs
- Visual Examinations of Oral Cavity
- BDI-II

Summaries of continuous parameters will include raw values and change from baseline, as appropriate. Listings of safety data will also be presented.

Analyses in this Section 10 will be based on data collected in Study TNX-CY-P306. Long-term safety analyses that span subject data from TNX-CY-P301, TNX-CY-P303, and TNX-CY-P306 are addressed in Section 12.

10.1 Adverse Events

All AEs will be coded using MedDRA, version 19.0.

Newly emergent adverse events (NEAEs) are defined as any new AE that started after the patient's first dose of study drug in Study TNX-CY-P306, or any unresolved AE first reported in Study TNX-CY-P301 or Study TNX-CY-P303 that exhibited an increase in severity, frequency or relationship after the patient's participation in Study TNX-CY-P306 had begun. For clarity, adverse events are classified as NEAEs based on a negative response to the CRF question "Did the AE start prior to the first dose?".

An AE summary table will be presented for the following:

- NEAEs by severity

- NEAEs leading to study drug discontinuation
- NEAEs by relationship
- SAEs
- Oral Cavity NEAEs

Summaries of incidence rates (frequencies and percentages) of individual AEs by MedDRA SOC and preferred term will be prepared. Such summaries will be displayed for all NEAEs, NEAEs by maximum severity, NEAEs by strongest relationship to study drug, and oral cavity NEAEs. Incidence of oral cavity NEAEs will be presented by category and preferred term, rather than SOC and preferred term.

Each participant will be counted only once within each summation level (SOC; preferred term). If a participant experiences more than one NEAE within each summation level only, the NEAE with the strongest relationship or the maximum severity, as appropriate, will be included in the summaries of relationship and severity.

Oral cavity adverse events will be defined by a custom MedDRA query (CMQ). These events will be further divided into 4 categories, as follows: 1) Sensory 2) Discomfort 3) Irritation/inflammation and 4) Lesions. Each category will be defined by a CMQ.

Additionally, a summary of the Oral Cavity AE characteristics will be presented; this includes information such as temporal proximity to the dose, duration and whether the AE was present the following morning. For purposes of this summary, only oral cavity NEAEs with the response "Yes" to the CRF question "Is AE in oral cavity"? will be included.

NEAEs pertaining to abuse potential will be reported by SOC and preferred term, and displayed in tabular format. Terms to be included may be found in Appendix 3.

In the AE data listings, all AEs collected in study TNX-CY-P306 will be displayed. AEs that are newly-emergent will be flagged.

10.1.1 Adverse Events Leading to Discontinuation of Study Drug

A summary of incidence rates (frequencies and percentages) of NEAEs leading to discontinuation of study drug by SOC and preferred term will be prepared for the Safety population.

A data listing of AEs leading to discontinuation of study drug will also be provided, displaying details of the event(s) captured on the CRF.

10.1.2 Serious Adverse Events

A summary of incidence rates (frequencies and percentages) of newly-emergent SAEs by SOC and preferred term will be prepared for the Safety Population. A data listing of all SAEs will also be provided, displaying details of the event(s) captured on the CRF.

10.1.3 Deaths

A listing of deaths will also be provided for the Safety Population.

10.2 Clinical Laboratory Evaluations

Laboratory data include analyses for Chemistry and Hematology and will be summarized by visit for the Safety Population. Descriptive summaries of actual values and change from baseline will be presented by study visit. 95% confidence intervals will be presented for change from baseline for each visit. ET data will be analyzed with the closest visit that does not have a valid assessment value.

Laboratory values will be displayed in the data listings and those that are outside the normal range ("H" or "L") will be flagged, along with corresponding normal ranges. Values pre-defined as potentially clinically significant ("HH" or "LL") will also be flagged. For each laboratory analysis, shifts in assessments of abnormality from baseline to each scheduled time point will be presented in shift tables.

A by-participant listing of all clinical laboratory data will also be provided.

10.3 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is an instrument that measures suicidal ideation and behavior. Items measuring suicidal ideation and suicidal behavior are displayed in the table below. Frequency counts of yes/no responses to items below and whether any suicidal ideation or behavior is present will be summarized as described below.

The overall number of participants with any suicidal ideation or behavior (by type and in total) or self-injurious behavior while on-treatment will be provided by treatment group. For ideation, participants will only be counted once at each visit and/or time frame at the worst-case response for ideation type (1-5), where 1 is the least severe and 5 is the most severe type of ideation.

Category	Items
A) Suicidal Ideation	(1) Type 1: Wish to be dead (2) Type 2: Non-specific active suicidal thoughts (3) Type 3: Active suicidal ideation with any methods (not plan) without intent to act (4) Type 4: Active suicidal ideation with any some intent to act, without specific plan (5) Type 5: Active suicidal ideation with specific plan and intent
B) Suicidal Behavior	(1) Preparatory acts or behavior (2) Aborted attempt (3) Interrupted attempt (4) Actual attempt (5) Completed suicide Suicidal Behavior present (composite of items 1-5) Non-Suicidal Self-Injurious Behavior

Suicidal intensity of ideation will be calculated by tallying up the five intensity items to create a total score ranging 0-25. If a participant does not have any suicidal ideation, a score of 0 will be given. Separate tables will be created for the entire Safety Population

as well as the population comprising only participants exhibiting any suicidal ideation. Suicidal intensity of ideation total score will be summarized using descriptive statistics by treatment group.

A data listing of C-SSRS results will include only participants with suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent. For participants with suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent at any time, data from all visits are displayed.

10.4 Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and change from baseline at each assessment time point and last on-treatment assessment will be calculated for vital signs including weight, BMI, body temperature, pulse rate, systolic blood pressure and diastolic blood pressure. 95% confidence intervals will be presented for change from baseline.

These summaries will be presented by assessment time for the Safety Population. ET data will be analyzed with the closest visit that does not have a valid assessment value.

10.5 Visual Examination of Oral Cavity

A visual examination of the oral cavity will be assessed at Baseline and Week 12. A visual examination is to be done any time a participant spontaneously reports an oral adverse event (aside from AEs known to be sensory-only, such as numbness, tingling or bitter taste) to confirm presence or absence of any signs of irritation or other visible abnormalities. A data listing of the visual examination results performed at each scheduled visit and at the time of an adverse event will be presented.

11. MEDICATIONS

11.1 Concomitant Medication

All medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) Version September 2016. Prior and concomitant medications will be summarized by treatment group and by the number and percentage of participants taking each medication, classified by using WHO-DD Anatomical Therapeutic Chemical Level 3 and preferred term.

Prior medications are defined as medications or therapies initiated prior to the start of the study drug and terminating prior to the start of study drug in protocol P301. Hence, these medications or therapies will have end dates prior to the first dose date of study drug. Concomitant medications are defined as any medications other than the study drug that a participant receives concurrently with the study drug. These medications will have end dates on or after the first dose date of the study drug until ten days after last dose date.

There should be no new prior medications recorded in protocol P306 as these should be captured entirely in P301. Concomitant medications will be summarized ATC Level 3 and preferred name. All medications will be presented in a listing.

Please refer to Section 7.3 for the conventions used to impute partial start dates and end dates of concomitant medications.

11.2 Exposure and Compliance

The treatment duration will be calculated as (number of days=last dose date — first dose date+1) and summarized. Participants that are lost to follow up or have a missing last dose date will be assigned a last dose date of the day before the last attended clinic visit for analysis purposes.

All pill count shortage (negative pill count) of greater than 4 doses (8 tablets) per 4-week assessment period and/or any between-visit compliance <70% will be considered protocol deviations, and the reason for the pill count discrepancy will be discussed with the participant and documented in the CRF to ensure that any cases of potential abuse or misuse are identified. Participants with more than one significant incidence of negative pill count discrepancy during the double-blind phase of the study will be closely monitored by the investigator.

Exposure in P306 will be measured using the last date of treatment and first date of treatment. Total exposure will be defined as the last date of treatment minus the first date of treatment plus one. The number of participants with total exposure by visit weeks (eg, 0 -12 weeks, >=12 – 24 weeks, >=24 – 36 weeks, >=36 – 48 weeks, and >=48 weeks) will be presented. Additionally, exposure days, defined as the total number of tablets taken divided by 2 (and rounded up to the nearest whole number), will be summarized.

Compliance will similarly be summarized across all study visits for each treatment arm. Study drug compliance as a percentage will be defined as the number of pills taken by the participant divided by the total number of pills that the participant was assigned to take multiplied by 100.

For calculating the compliance and exposure days, the following convention will be applied: for periods where drug is issued, but the participant does not return any bottles or tablets, or the participant misses the visit entirely, that period will not contribute to the compliance or exposure calculation unless the bottles are returned at a later visit.

Compliance will be summarized with descriptive statistics by treatment arm. The number and percentages of participants within certain categories of compliance e.g. <50%, 50% to <70%, 70% to ≤100%, >100% will be presented. Compliance between 70% to 114% will not be considered a protocol deviation. Tablet counts, calculation of compliance overall and by visit, and participant-reported reasons for all tablet discrepancies at all visits will be presented in a listing.

In addition, participants with significant over-usage or otherwise unaccounted-for missing tablets resulting in >114% compliance for any visit (e.g., failure to return >8 tablets per 4 week interval) will be summarized by visit and overall. These listings will include both the participant-reported reason for the discrepancy plus the investigator's assessment of potential abuse, misuse or diversion. Clinically significant drug accountability discrepancies associated with missing medication, loss of drug, or cases in which the PI confirms concern over drug abuse, misuse or diversion, will be examined and discussed in the CSR.

12. LONG-TERM SAFETY ANALYSES

Select safety analyses will be conducted on the data collected across Studies TNX-CY-P301, TNX-CY-P303, and TNX-CY-P306 (the "long-term analysis period"). For purposes of clarity, only subjects in the TNX-CY-P306 Safety Population are included in these analyses, except where specified in Section 12.1. The purpose of this set of analyses is to support the long-term safety profile of TNX-102 SL 5.6 mg per day. Certain definitions and analyses in this Section 12 may differ from that of other sections in this SAP.

All analyses will be summarized for the TNX-102 SL group only, except where specified in Section 12.1. For subjects who were treated with placebo in Study TNX-CY-P301, analyses will exclude the subject data from Study TNX-CY-P301 (except to the extent the baseline record may come from Study TNX-CY-P301, as applicable). For purposes of Sections 12.3 and 12.4, baseline is the last assessment prior to dosing with TNX-102 SL for the first time.

12.1 Long-Term Disposition

The numbers and percentage of subjects who received study drug in each study, completed each study, and withdrew from each study will be tabulated, by treatment sequence and overall. The number and percentage of subjects in each unique study sequence will also be tabulated. This summary will be created once for the TNX-CY-P301 Safety Population (ie, any subject who dosed in TNX-CY-P301) and repeated for the TNX-CY-P306 Safety Population (ie, any subject who dosed in TNX-CY-P306).

12.2 Long-Term Adverse Events Analyses

For purposes of the long-term AE analyses, treatment-emergent AEs (TEAEs) are any AE with an onset at the time of or following the start of treatment in any of the 3 studies (TNX-CY-P301, TNX-CY-P303, and TNX-CY-P306). To align with the study-level CSR, any AE identified as a TEAE in the study-level CSR for study TNX-CY-P301 will be deemed a TEAE.

Analyses of TEAEs will be presented only for the TNX-102 SL group. Specifically, for subjects who were actually treated with placebo in Study TNX-CY-P301, any TEAEs collected in Study TNX-CY-P301 would be disregarded; only TEAEs that are newly-emergent in Studies TNX-CY-P303 or TNX-CY-P306 would be included. For subjects treated with TNX-102 SL in Study TNX-CY-P301, any AE identified in either the TNX-CY-P303 or TNX-CY-P306 database will be deemed treatment-emergent and eligible for inclusion in analyses, unless the start date is collected and is prior to the treatment start date in TNX-CY-P301.

An overall summary of AEs will summarize the number and percentage of subjects with any TEAE, nonfatal serious TEAE, TEAE leading to death, TEAE by maximum severity, TEAE by maximum relationship, TEAE leading to dose interruption, TEAE leading to dose reduction, TEAE leading to study drug discontinuation, or oral cavity TEAE (see definition below in this section) by category, in the long-term analysis period.

The following analyses of TEAEs will be completed:

- Overall summary of TEAEs

- Incidence of TEAEs by SOC and preferred term
- Incidence of serious TEAEs by SOC and preferred term
- Incidence of TEAEs leading to study drug discontinuation by SOC and preferred term
- Incidence of oral cavity TEAEs by category and preferred term
- Incidence of serious oral cavity TEAEs by category and preferred term
- Incidence of oral cavity TEAEs leading to study drug discontinuation by category and preferred term
- Incidence of TEAEs potentially suggestive of abuse by SOC and preferred term

Oral cavity TEAEs are defined in Section 10.1. TEAEs are identified as potentially suggestive of abuse based on the preferred terms listed in Appendix 3. Of note, somnolence and sedation are known and expected cyclobenzaprine drug effects; these preferred terms will still be included in these displays, if present.

In addition, the incidence of patients with each category of oral cavity TEAEs will be summarized by increments based on the relative start day of the AE compared to first dose of active drug in any study (0-12 weeks, >12-24 weeks, >24-36 weeks, >36-48 weeks, and >48 weeks). Intervals may be changed for more meaningful interpretation based on the actual distribution of the AE data. For each increment, the denominator will be the number of subjects with risk-time extending into that time interval, specifically, with a duration of exposure to TNX-102 SL of at least the lower limit of that increment. For instance, the number of subjects with >12 weeks of exposure would be the denominator for the >12-24 week increment. Duration of exposure is defined in Section 12.5). The last dose date is the last dose date in Study TNX-CY-P306, and the first dose date is the first dose of TNX-102 SL in any study. If a subject experienced more than one TEAE in a given category, the first event will be selected.

A similar analysis will be provided for the incidence of TEAEs and serious TEAEs by SOC and preferred term.

12.3 Long-Term Vital Signs Analyses

Descriptive summaries of actual values and change from baseline to the minimum post-baseline value, maximum post-baseline value, and final value in the long-term analysis period will be summarized for weight, BMI, body temperature, pulse rate, systolic blood pressure and diastolic blood pressure.

Clinically notable vital signs in the long-term analysis period will be identified based on the criteria below. The number and percentage of subjects with at least 1 treatment-emergent value (i.e., not present at baseline) meeting the criteria below will be tabulated, using the worst post-baseline value in either direction.

Clinically Notable Vital Sign Categories

Vital Sign Parameter	Value
Heart rate	≥130 bpm
	<55 bpm
Systolic Blood Pressure	≥160 mg Hg
	≤90 mm Hg

Diastolic blood pressure	≥100 mg Hg ≤60 mm Hg

bpm = beats per minute

12.4 Long-Term Clinical Laboratory Evaluations

Descriptive summaries of actual values and change from baseline to the minimum post-baseline value, maximum post-baseline value, and final value in the long-term analysis period will be summarized for chemistry and hematology parameters.

A summary of treatment emergent shifts will compare the baseline L/N/H classification for each laboratory test to the highest and/or lowest L/N/H classification post-baseline in the long-term analysis period.

Additionally, subject counts of any post-baseline elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and alkaline phosphatase (ALP) will be presented in a separate table, as follows.

Table 7-1 Elevated Liver Function Test Categories

Clinical Laboratory Parameter	Category
ALT	≥3 × ULN; ≥5 × ULN
AST	≥3 × ULN; ≥5 × ULN
ALT or AST	≥3 × ULN; ≥5 × ULN
ALP	≥1.5 × ULN
Total bilirubin	≥ULN; ≥2 × ULN
Total bilirubin elevation with ALT or AST elevation at any post-baseline timepoint(s)	(ALT or AST ≥3 × ULN) and (total bilirubin ≥2 × ULN)
Concurrent total bilirubin elevation with ALT or AST elevation and ALP <2 × ULN [1] ("potential Hy's law cases")	(ALT or AST ≥ 3 × ULN) and ALP <2 × ULN and (total bilirubin ≥2 × ULN)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal
[1] Concurrent means on the same date.

Potential Hy's law cases (based on the recommendation in "Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation") will be identified as subjects with post-baseline ALT or AST ≥3 x upper limit of normal (ULN) and total bilirubin ≥2 x ULN and ALP <2 × ULN on the same date, as noted above. Liver function test data on any subjects with ALT or AST ≥3 × ULN will be listed, and any potential Hy's law cases will be specifically identified.

To assess cases potentially meeting requirements for Hy's Law, an evaluation of drug-induced serious hepatotoxicity plot of bilirubin against peak ALT will be generated by treatment group, as described by Watkins et al (2008). This plot will be reproduced for

peak AST vs. peak total bilirubin, as well as for the greater of peak AST and peak ALT vs. peak total bilirubin.

12.5 Long-Term Exposure

Summary statistics will be presented for duration of exposure (days and weeks) in the long-term analysis period, defined as the [last dose date of TNX-102 SL – first dose date of TNX-102 SL + 1], for TNX-102 SL. Duration of treatment (weeks) will also be summarized as categorical measures (eg, 0 -12 weeks, >=12 – 24 weeks, >=24 – 36 weeks, >=36 – 48 weeks, and >=48 weeks).

13. CHANGES FROM PLANNED ANALYSIS

Study day as it appears in data listings and the Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets will differ from the protocol: The protocol describes the day of first dose as “Day 0”; the listings and datasets will conform to the standard of first dose day appearing as “Day 1”.

14. REFERENCES

Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), February 2010.

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Davidson J, Rothbaum BO, Tucker P, Asnis G, Benattia I, Musgnung JJ. Venlafaxine extended release in posttraumatic stress disorder: a sertraline- and placebo-controlled study. J Clin Psychopharmacol. 2006;26(3):259-67.

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Sheehan KH & Sheehan DV. Assessing treatment effects in clinical trials with the Discan metric of the Sheehan Disability Scale. Int Clin Psychopharmacol 2008:23:70-83.

Watkins PB, Seligman PJ, Pears JS, Avigan MI, Senior JR. Using Controlled Clinical Trials to Learn More About Drug-Induced Liver Injury. Hepatology. 2008, 48:1680-1689.

Weathers FW, Blake DD, Schnurr PP, Kaloupek DG, Marx, et al. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). 2013: Instrument available from the National Center for PTSD at www.ptsd.va.gov.

15. APPENDICES

15.1 Appendix 1

The following reporting conventions will be adopted for the presentation of study data. These conventions will enhance the review process and help to standardize presentation with common notations.

15.1.1 General Reporting Conventions

- All tables and data listings will be developed in Landscape Orientation, unless presented as part of the text in a clinical study report (CSR).
- Figures will be presented in Landscape Orientation, unless presented as part of the text in a CSR.
- Legends will be used for all figures with more than one variable or item displayed.
- Figures will be in black and white, unless color figures have been identified as useful for discriminating presentation in the figure. Lines in figures should be wide enough to view the line after being photocopied.
- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as non-printable control characters, printer specific, or font specific characters, will not be used on a table, figure, or data listing. Hexadecimal character representations are allowed (e.g., μ, α, β).
- All titles will be centered on a page. The ICH numbering convention is to be used for all tables, listings, and graphs (TLGs).
- All footnotes will be left justified at the bottom of a page. Footnotes must be present on the page where they are first referenced. Footnotes should be used sparingly and must add value to the TLG. If more than four footnote lines are planned then a cover page may be used to display footnotes.
- Missing values for both numeric and character variables will be presented as blanks in a table or data listing. A zero (0) may be used if appropriate to identify when the frequency of a variable is not observed.
- All date values will be presented as YYYY-MM-DD (e.g., 2001-10-17) format. A four-digit year is preferred for all dates.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study.
- Time durations will be reported in mixed HHhr MMm SSs notation (e.g., 5h 32m, or 27h 52m 31s). The use of decimal notation to present (display) time

durations should be avoided (e.g. 0.083h = 5m) unless it is necessary to show the computation of time differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.

- All TLGs will have the name of the program, location, programmer, and a date stamp on the bottom of each output.
- All analysis programs developed for a TLG display will be self-contained to facilitate transfer of programs to multiple computing environments and transfer to a regulatory agency (if requested).

15.1.2 Population Summary Conventions

- Population(s) represented on the tables or data listings will be clearly identified in the last title of the Table as "<name of population>" and will be identical in name to that identified in the protocol or SAP.
- Consistent terminology will be used to define and identify a population. Common nomenclature may include (a) All Participants, (b) ITT, (c) Safety, and (d) PP.
- Sub-population(s) or special population(s) descriptions will provide sufficient detail to ensure comprehension of the population (e.g., MITT >60 years of age) used for analysis in a table or figure.
- Population sizes may be presented for each treatment or dosing category as totals in the column header as (N=xxxx), where appropriate.
- Population sizes shown with summary statistics are the samples sizes (n) of Participants with non-missing values.
- All population summaries for categorical variables will include all categories that were planned and for which the Participants may have had a response. Percentages corresponding to null categories (cells) will be suppressed.
- All population summaries for continuous variables will include: n, mean, SD, minimum, and maximum. Other summaries (e.g. number missing, median, quartiles, 95% confidence intervals, CV or %CV) may be used as appropriate.
- All percentages are rounded and reported to a single decimal point (xx.x%). A percentage of 100% will be reported as 100%. A percentage of zero will be reported as 0.
- Population summaries that include *P* values will report the *P* value to three decimal places with a leading zero (0.001). All *P* values reported on default output from statistical software (i.e., SAS® Software) may be reported at the default level of precision. *P* values <0.001 should be reported as <0.001 not 0.000.

15.2 Appendix 2: PROMIS T-score Conversions

Sleep-Related Impairment 8a *Short Form Conversion Table*		
Raw Score	**T-score**	**SE***
8	30.0	5.4
9	35.1	4.6
10	38.7	4.2
11	41.4	3.8
12	43.6	3.6
13	45.5	3.4
14	47.3	3.1
15	48.9	2.9
16	50.3	2.7
17	51.6	2.6
18	52.9	2.6
19	54.0	2.5
20	55.1	2.5
21	56.1	2.5
22	57.2	2.5
23	58.2	2.4
24	59.3	2.4
25	60.3	2.4
26	61.3	2.4
27	62.3	2.3
28	63.3	2.3
29	64.3	2.3
30	65.3	2.3
31	66.3	2.3
32	67.3	2.3
33	68.4	2.3
34	69.5	2.4
35	70.7	2.4
36	71.9	2.5
37	73.3	2.6
38	75.0	2.8
39	76.9	3.1
40	80.0	3.9

*SE = Standard Error on T-score metric

15.3 Appendix 3: Abuse Terms

The following preferred terms will be used to identify AEs potentially related to abuse.

Category	MedDRA Preferred Term
Central nervous system depression terms	Bradyphrenia
	Depression
	Dysphoria
	Hypersomnia
	Hypersomnia related to another mental condition
	Infant sedation
	Neonatal oversedation
	Post-injection delirium sedation syndrome
	Sedation*
	Sedation complication
	Sedative therapy
	Somnolence*
	Somnolence neonatal
	Stupor
Central nervous system stimulation terms	Affect lability
	Aggression
	Agitation
	Anxiety
	Disinhibition
	Energy increased
	Feeling jittery
	Flight of ideas
	Hypervigilance
	Irritability
	Psychomotor hyperactivity
	Restlessness
Dissociative/psychotic-related terms	Abnormal behaviour
	Acute psychosis
	Amnesia
	Delirium
	Delusion
	Delusion of grandeur
	Delusional perception
	Depersonalisation
	Depersonalisation/derealisation disorder
	Derealisation
	Disturbance in attention

	Hallucination
	Hallucination, auditory
	Hallucination, gustatory
	Hallucination, olfactory
	Hallucination, synaesthetic
	Hallucination, tactile
	Hallucination, visual
	Hallucinations, mixed
	Hypnagogic hallucination
	Hypnopompic hallucination
	Mixed delusion
	Psychotic disorder
	Sensory disturbance
	Substance-induced psychotic disorder
	Thinking abnormal
	Transient psychosis
Euphoria-related terms	Elevated mood
	Euphoric mood
	Feeling drunk
	Feeling of relaxation
General terms	Dependence
	Drug abuse
	Drug abuser
	Drug dependence
	Drug dependence, antepartum
	Drug dependence, postpartum
	Drug diversion
	Drug use disorder
	Drug use disorder, antepartum
	Drug use disorder, postpartum
	Drug withdrawal convulsions
	Drug withdrawal headache
	Drug withdrawal maintenance therapy
	Drug withdrawal syndrome
	Drug withdrawal syndrome neonatal
	Substance abuse
	Substance abuser
	Substance dependence
	Substance use disorder
	Withdrawal arrhythmia
	Withdrawal catatonia
	Withdrawal hypertension

	Withdrawal syndrome
Terms not captured elsewhere	Confusional state
	Disorientation
	Emotional disorder
	Feeling abnormal
	Homicidal ideation
	Inappropriate affect
	Intentional misuse of drug delivery system
	Intentional product misuse
	Logorrhoea
	Mania
	Memory impairment
	Mental disorder
	Mood altered
	Mood disorder due to a general medical condition
	Mood swings
	Overdose
	Prescription form tampering
	Product tampering
	Substance-induced mood disorder
	Suicidal ideation
	Suspected product tampering

*Anticipated drug effects

Note: Terms are adapted from the list in Steven Galati's presentation (Galati 2023.)